



Case report

A fatal case of streptococcal and meningococcal meningitis in a 2-years-old child occurring as Waterhouse–Friderichsen Syndrome



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ARTICLE INFO

Article history:

Received 8 February 2013

Received in revised form

28 March 2013

Accepted 9 April 2013

Available online 28 April 2013

Keywords:

Fatal streptococcal-meningococcal

co-infection

Meningitis

Waterhouse–Friderichsen Syndrome

Professional liability profiles

ABSTRACT

We report a fatal case of streptococcal and meningococcal meningitis in a previously healthy 2-year-old child, a simultaneous co-infection of both pathogens that is poorly reported in the reviewed literature. The lack of a clinical diagnosis in addition to the medico-legal aspects arising from possible professional liability for the emergency service doctor who had failed to recognize the child's symptoms led to a forensic autopsy within 48 h after the death. After external and internal examination, Waterhouse–Friderichsen Syndrome (WFS) was suspected. Consequently, cerebrospinal fluid, whole blood, nasal and pharyngeal swab and pleural liquid samples were selected and collected for microbiological studies. All tested samples resulted *Neisseria meningitidis* DNA and *Streptococcus pneumoniae* DNA positive. The NM genotyping Real-Time PCR resulted positive for NM serotype C. Microscopic histological study confirmed these findings.

We underline that when a patient presents fever and *petechiae* (50–60% of patients), WFS must be considered, even when the patient has a non-toxic appearance. Due to its rapid progression and often devastating consequences, therapy should be started as soon as WFS is suspected.

Emphasis should also be placed on the importance of public education programs and on broadening protection against meningitis through new vaccines.

In such cases, from a forensic point of view, there is a strong need for a robust, multidisciplinary approach in order to reach the correct post-mortem diagnosis.

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1. Introduction

Bacterial meningitis is often a serious and potentially fatal infection that affects the central nervous system, especially in infants.¹ *Streptococcus pneumoniae* and *Neisseria meningitidis* are among the main causes of these infections.² However, the co-infection of both the pathogens is poorly reported in the reviewed literature.

The onset is often insidious and consequently a late diagnosis is quite common, often after death, when the so-called Waterhouse–Friderichsen Syndrome (WFS) appears.^{3,4}

Also known as “*purpura fulminans*”, onset is characterized by an acute and massive hemorrhagic necrosis of the adrenal glands in

the setting of an ongoing clinical sepsis, most often caused by a meningococcal infection. The literature however reports cases of WFS determined by *pneumococcus*⁵ as well as by other pathogens.⁶ This clinical entity is more frequently seen in the pediatric rather than the adult population and is associated with high morbidity and mortality.

We present a case of WFS in a previously healthy two-year-old child with meningitis symptoms leading to septicemia and death caused by meningococcal and streptococcal co-infection.

2. Case report

A nine year-old child had been suffering for 24 h from high fever (40°), vomiting, and a red/black rash on her hands and under her feet without any response to drugs.

Her two-year-old cousin (male), who had been staying with her during the Christmas holidays, had also suffered from a high

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temperature (38.5°), but for a shorter period of time (12 h). He too was unresponsive to drugs. Due to her worsening clinical condition, at 9.40 pm the girl's parents decided to call the emergency service. After examining the girl, the emergency service doctor found a rash which, in his diagnosis, was determined by food poisoning. He prescribed paracetamol (acetaminophen). The doctor was also asked to examine the little boy, on whom he found a swelling of the retronasal gland, which was not considered significant. Again, the doctor suggested the same therapy (paracetamol). A few hours later, during the night (4.30 am), the girl's parents found the infant thirsty and puffy with black spots on the face and the body. They immediately called the ambulance service and he was taken to a local hospital. Arriving at the hospital at around 5.40 am, due to the long distance, the infant was admitted to the intensive care unit with a diagnosis of "suspected sepsis". On examination the clinicians reported: "... Stupor, responding to painful stimuli, hypotonic, hemorrhagic skin lesions, no peripheral pulses palpable ... hypothermic with peripheral vasoconstriction, neck stiffness, Lasegue negative".

Accordingly, the doctors placed a venous access with a left external jugular vein cannulation, performed assisted ventilation and hydration, administered ceftriaxone, dexamethasone and dopamine. The infant was then moved to the Regional Pediatric Center with a "Red Code" classification (the most serious in the triage scale).

Concurrently, the girl was also transferred to the same Regional Pediatric Center with the less serious "yellow code" (medium degree of the triage scale) due to better clinical conditions.

On arrival (7.30 am) "septic shock (suspected meningococemia)" was diagnosed for the baby, who soon suffered cardiac arrest, presenting "confluent ecchymosis-like lesions spread to the whole body, vasoconstricted peripheral circulation, areflexia, mydriatic

and areactive pupils". He was intubated and ventilated but 45 min later, in spite of all resuscitation attempts, he suffered "irreversible cardiac arrest due to meningococcal sepsis, hemorrhagic symptoms, septic shock, suspect cerebral hemorrhage".

The case is of medico-legal significance due to the professional liability issues in question. In fact, public prosecutor (*Pubblico Ministero*) alleged that the doctor of the emergency service had underestimated the seriousness of the infant's symptoms, which in addition to the delay in reaching the hospital, contributed to reducing the infant's possibility of survival.

3. Material, methods and results

3.1. Autopsy findings

An autopsy was performed within 48 h after death. As the clinical data suggested meningococemia cerebrospinal fluid (CSF), nasal and pharyngeal swabs were carefully selected and collected for microbiological studies. As suggested in literature,⁷ an accurate lumbar puncture was performed before the beginning of autopsy in order to minimize the risks of hemorrhagic and/or bacterial contamination of (CSF) samples.

External examination revealed a normal development of the baby related to his age; purple marbling had spread to the face, limbs, the anterior region of the chest, abdomen and thighs to the root (Fig. 1A, B).

Internal examination showed the absence of epidural, subarachnoid, and arachnoid hemorrhage, though the leptomeninges were thin and congested; there was also a marked edema of the brain.

Cerebrospinal fluid appeared cloudy. Few cc of citrine liquid were found in both pleural cavities. During sections, foamy material came out of the lungs, which were also congested.

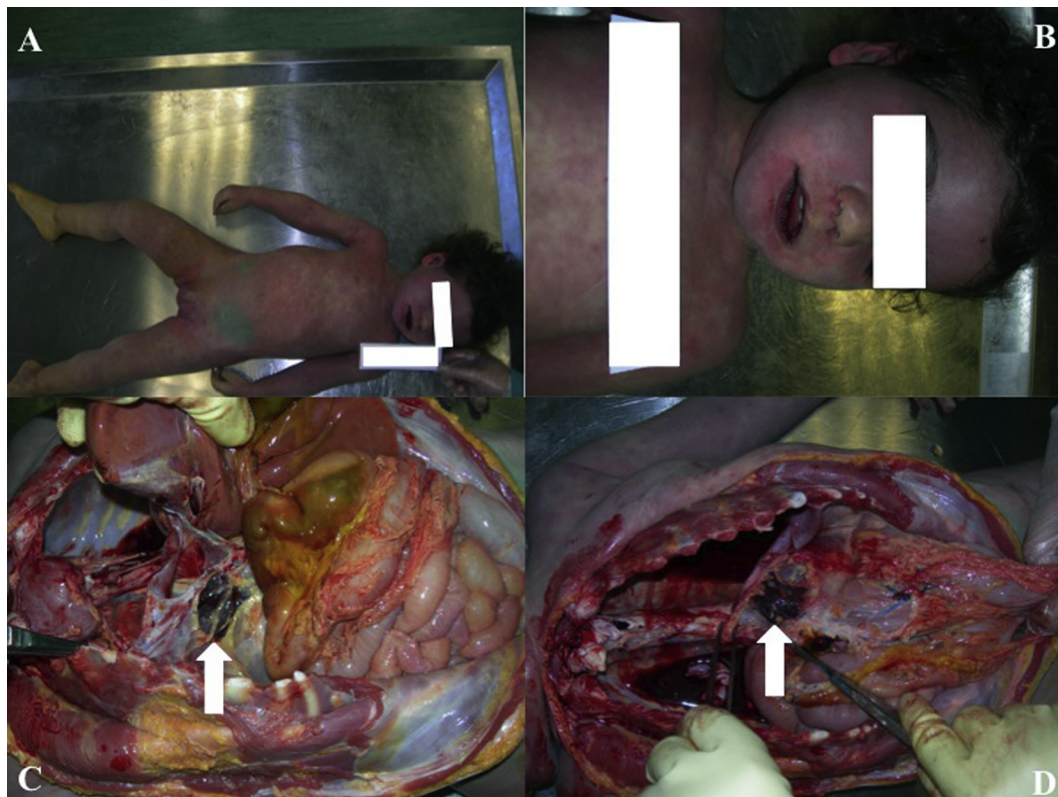


Fig. 1. Purple marbling spreading to the face, limbs, the anterior region of the chest, abdomen and thighs to the root. A: whole body; B: focus on the face; C–D: *in situ* adrenal glands showing hemorrhagic infiltration of the parenchyma. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Epicardium presented diffuse *petechiae* on the anterior wall. Adrenal glands showed a hemorrhagic infiltration of the parenchyma (Fig. 1C, D). Multi-organ vascular congestion was found.

No other pathological findings were observed.

Blood samples and pleural liquid were taken for analysis.

3.2. Histological findings

The microscopic histological study, performed by using formalin-fixed paraffin embedded tissue sectioned at 4 μ m and stained with hematoxylin-eosin (H&E), confirmed the macroscopic findings. Particularly, it showed:

- ▲ Brain: mild inflammatory infiltration with prevalence of lymphocytes and presence of sporadic granulocytes at leptomeningeal and perivascular level (Fig. 2);
- ▲ Lungs: marked congestion, mild emphysema and focal subatelectasia; presence of neutrophils and lymphocytes at vessels walls and peribronchial level (Fig. 3);
- ▲ Adrenal glands: diffuse hemorrhagic infiltration without any aspect of inflammation (Fig. 4);
- ▲ Multi-organ vascular congestion.

All these findings suggested Waterhouse–Friderichsen Syndrome owing to acute meningitis with diffuse hemorrhagic infiltration of the adrenal glands.

3.3. Microbiological studies

Aliquots of each sample were inoculated onto blood and chocolate agar plates and in thioglycolate enrichment broth and incubated for 48–72 h at 35 °C with 5% CO₂.

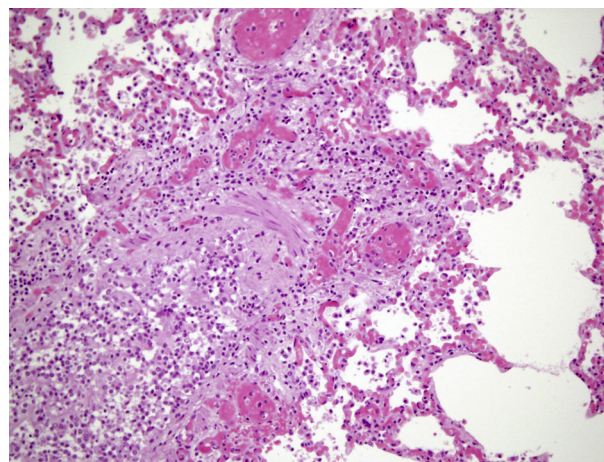


Fig. 3. Lungs: marked congestion, mild emphysema and focal subatelectasia; presence of neutrophils and lymphocytes at vessels walls and peribronchial level (20 \times H&E).

Total DNA was extracted using the High Pure PCR Template Preparation Kit (Roche) manual extraction system following the manufacturer's instructions and DNA was eluted in a final volume of 60 μ l.

Real-time PCR assays were performed using the LightCycler instrument (Roche). For *N. meningitidis* (NM) detection a commercial kit was used (Neisseria meningitidis Lcset, TibMolbiol) whilst for *S. pneumoniae* (SP) and NM genotyping specific primers and probes were used as described previously.^{8,9}

To control the course of extraction and check for PCR inhibitors, a fragment of the *Homo sapiens* Beta-Globin gene was amplified.

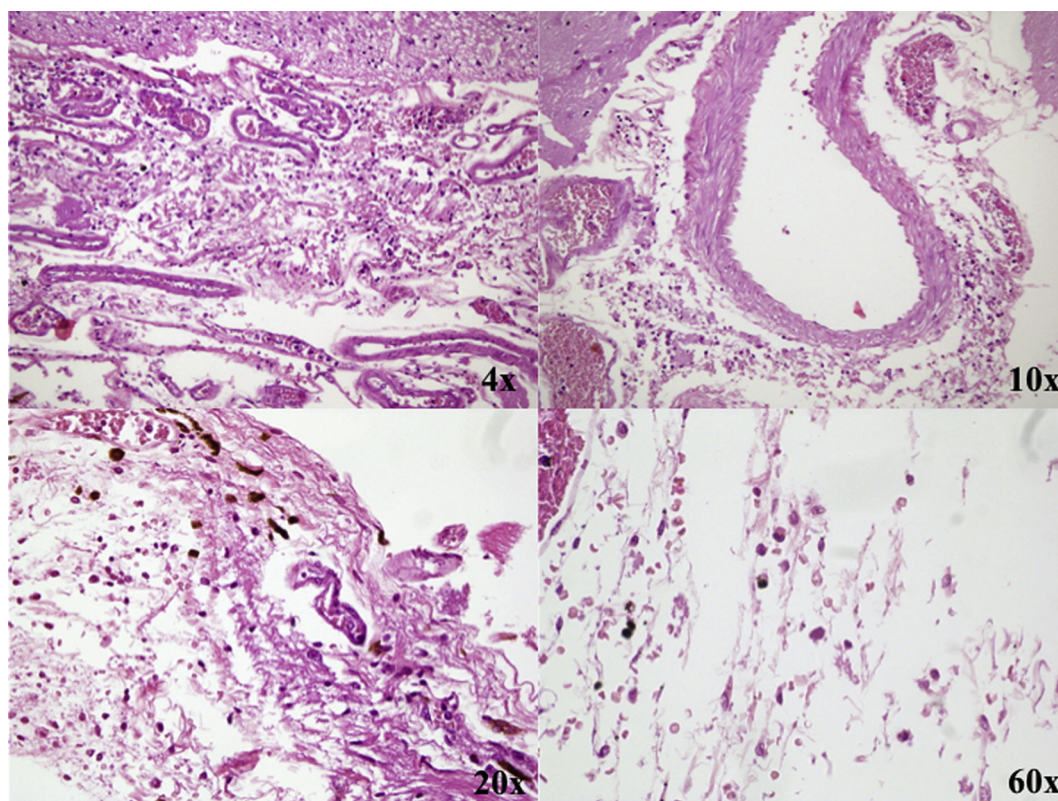


Fig. 2. Brain: mild inflammatory infiltration with prevalence of lymphocytes and presence of sporadic granulocytes at leptomeningeal and perivascular level (increasing magnification: 4 \times , 10 \times , 20 \times , and 60 \times H&E).

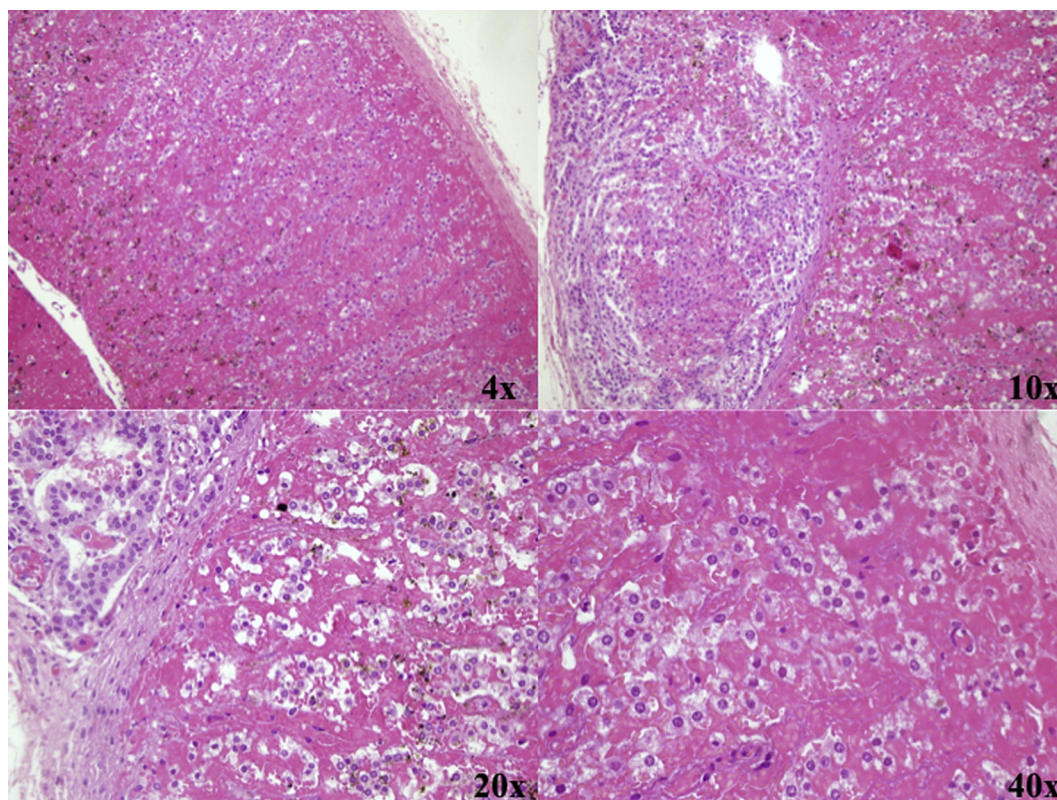


Fig. 4. Adrenal glands: diffuse hemorrhagic infiltration without any aspect of inflammation (increasing magnification: 4×, 10×, 20×, and 40× H&E).

All samples tested resulted NM DNA and SP DNA positive. The NM genotyping PCR resulted positive for NM serotype C and negative for serotypes A and B.

The positivity for Beta-globin demonstrated that the DNA extraction procedure was efficient in extracting amplifiable DNA from the sample.

The same samples were instead culture negative after 72 h incubation.

According to all the above-mentioned studies, the cause of death was attributed to “septic shock due to meningitis caused by *meningococcus* and *pneumococcus* identifiable as Waterhouse–Friderichsen Syndrome”.

4. Discussion

Acute bacterial meningitis (ABM) continues to be associated with high mortality and morbidity, despite advances in antimicrobial therapy.

The literature reports that antibiotics now reduce mortality of acute bacterial meningitis by up to 10% in the event of timely diagnosis.¹⁰

The causative organism varies with age, immune function, immunization status, and geographic region, and empiric therapy for meningitis is based on these factors.

The three major pathogens causing bacterial meningitis are *N. meningitidis*, *S. pneumoniae* and *Haemophilus influenzae* type B (Hib).¹

Disease epidemiology is changing rapidly due to immunization practices and changing bacterial resistance patterns. Recently, vaccines have also been introduced for pneumococcal and meningococcal infections, which have significantly changed the disease profile. However, antibiotic resistance is an increasing problem, especially with pneumococcal infection.¹¹

Late diagnosis of meningitis, especially among the very young, is often fatal. The survival rate drops further in the presence of Waterhouse–Friderichsen Syndrome. Meningeal infections with septicemia are usually suspected on the basis of clinical symptoms such as fever, vomiting, neck stiffness, and skin rash (purpura). In addition, in the case of WFS, hypoglycemia with hyponatremia and hyperkalemia could appear as a consequence of the acute adrenal failure.

Rapid accurate diagnosis is essential for optimal patient management and the provision of prompt prophylaxes to contacts.

In the presented case, although the emergency practitioner had at his disposal the means to observe many of the above-mentioned symptoms on the girl, the seriousness of her condition was underestimated and consequently so was the baby's.

The latter, due to a very rare and fatal co-infection and probably due to the less developed immune system, presented an extremely rapid progression of the disease till the *exitus*.

In fact, apart from recent insights emerging in the literature relating to individual susceptibility, one single infection could have probably increased the chances of the infant's survival as demonstrated by the different outcome of his older cousin, who resulted positive only for *N. meningitidis*.

Specifically, no cases of deaths following meningitis due to Meningococcal and Streptococcal co-infection, similar to the one presented, have previously been described in the literature reviewed.

During the evaluation of professional liability the doctor was found guilty of incompetence (“inexperienced for not recognizing a typical manifestation of such a serious and, at the same time, not rare infection, as well as negligent and reckless for not having recommended the immediate transfer to hospital in order to perform further investigations” the Public Prosecutor's Consultant said).

Particularly, he should immediately transfer both the girl and the baby to the closer Pediatric Center where they could be timely treated. As a matter of fact, the pathognomonic and, at the same time, misunderstood clinical pattern made the failure to reach the correct diagnosis really unforgivable.

He was not found guilty of manslaughter, however, as it could not be proved that a timely diagnosis and prompt therapy could have led to the infant's life being saved. Such an outcome was determined by the absence of a specific provision in the Italian Criminal Code on the question of medical liability. In this sense, we are aware of only two civil-law countries (Libya and the United Arab Emirates) where specific healthcare-related criminal laws are in force.

5. Conclusion

We underline that, when a child has high fever and *petechiae* (50–60% of patients as reported by Varon et al.),¹² WFS must be considered, even though the patient has a non-toxic appearance. Due to the rapid progression and often devastating consequences, therapy should be started as soon as meningitis is suspected.

Particularly, emergency practitioners should understand and recognize the signs and symptoms of serious meningococcal disease, especially in the very young, and refer children to pediatric services immediately.¹³

In this sense we would like to share with the scientific community the evidence of PCR testing as an available, extremely helpful tool to be used every time a specific microbiological diagnosis should be promptly performed.

At the same time, in a public health perspective, as widely illustrated in the literature, we also stress the importance of public education programs and of greater protection against meningitis through new vaccines, as well as the need for multicentric studies that seek to identify possible factors of individual susceptibility to an increasing number of fatal infections also in the industrialized world.

From a forensic point of view, we support a robust multidisciplinary approach in order to reach the correct post-mortem diagnosis, especially when professional liability is suspected.^{14,15}

Particularly, microbiological studies, which are routinely not performed, become mandatory in cases similar to the presented one, where the histological brain pattern was not enough suggestive for the bacterial origin of meningitis. In our experience, they are found to be reliable if conducted up no later than 72 h after death. On this point, we would like to highlight again the importance of PCR because of its higher sensitivity and specificity compared to standard bacteriology.^{16,17}

Last but not least, in the light of the limited number of reports in the literature, this paper seeks to widen knowledge in the area of peculiar fatal co-infections.

Ethical approval

None.

Funding

None.

Conflict of interest

The authors had no financial and personal relationships with other people or organisations that could inappropriately influence our work. Accordingly, we declare that we have no conflicts of interest.

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